



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/715,329	11/17/2003	Yingming Zhao	UTSD:1489US	5752
32425	7590	09/08/2005	EXAMINER	
FULBRIGHT & JAWORSKI L.L.P. 600 CONGRESS AVE. SUITE 2400 AUSTIN, TX 78701			VENCİ, DAVID J	
			ART UNIT	PAPER NUMBER
			1641	

DATE MAILED: 09/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

10/715,329

Applicant(s)

ZHAO ET AL.

Examiner

David J. Venci

Art Unit

1641

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on July 6, 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-32 is/are pending in the application.
- 4a) Of the above claim(s) 8, 10 and 30-32 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-7, 9 and 11-29 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☒ Claim(s) 1-32 are subject to restriction and/or election requirement.

### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

Art Unit: 1641

### **DETAILED ACTION**

Examiner acknowledges Applicants' reply, filed July 6, 2005, which amended claims 1-2, 19 and 24-29. Claims 8, 10 and 30-32 were withdrawn from consideration pursuant to 37 CFR 1.142(b) as being drawn to non-elected inventions or species.

Currently, claims 1-7, 9 and 11-29 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### ***Specification***

The disclosure is objected to because of the following informalities:

On p. 12, line 5, reference to "equation 2" is indefinite because Examiner is unable to locate "equation 2" in Applicants' specification.

Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112***

Claims 1-7, 9 and 11-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Art Unit: 1641

In claim 1, step (a), the recitation of "isoprenyl azide substrate of at least a first protein" is grammatically awkward and indefinite because it is not clear whether said "substrate" describes a substrate for said "azide" entity, or whether said "substrate" describes a substrate for said "protein" entity.

In claim 1, step (b), the recitation of "incorporates into the first protein at least the first azide" is indefinite because it is not clear whether/how a protein "incorporates" an azide moiety. It is not clear whether an azide moiety is synthesized *de novo* on "the first protein" or whether the first protein is reacted with the first azide moiety.

In claim 1, step (c), the recitation of "proteins produced by said cell with a phosphine capture reagent" is indefinite because it is not clear how cells produce proteins "with a phosphine capture reagent." It is not clear whether the cell is contacted with "a phosphine capture reagent," or whether the cell produces "a phosphine capture reagent" endogenously. In addition, the recitation of "proteins produced by said cells... by the Staudinger reaction" is indefinite because it is not clear how cell produce proteins by performing "the Staudinger reaction." In addition, the recitation of "detecting at least said first protein... with a phosphine capture reagent" is indefinite because it is not clear whether said first protein is contacted with a phosphine moiety, or whether said first protein is produced with a phosphine moiety by said cell.

In claims 4-6, the recitation of "FPP" lacks antecedent basis. In claims 5-6, it is not clear how "HMG Co-A reductase inhibitor" and "lovastatin" inhibit FPP.

In claim 28, step b), the recitation "the synthetic substrate is... incorporated into the protein" is indefinite because the recited molecular structures do not appear to be "incorporated into the protein" as required in line 2 of step b). The presence of "the protein" in the molecular structures recited in step b) is not readily apparent. The mechanism or step(s) required for incorporation is not clear. In addition, the recitation of "the protein is labeled with said first azide" is indefinite because the molecular structures recited in step b)

Art Unit: 1641

appear to have intact azido moieties with no attachment to "the protein". It is not clear how "said first azide" functions as a label. The mechanism or step(s) required for labeling is not clear.

In claim 29, the recitation of "the synthetic substrate... is prenylated" is indefinite because it is not clear how, or by what mechanism, the synthetic substrates having the molecular formulas recited in claim 28, step b), are "prenylated".

***Claim Rejections - 35 USC § 103***

Claims 1-7, 9, 11, 13 and 15-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spielmann et al. (US 6,284,910) in view of Saxon & Bertozzi (US 6,570,040).

Spielmann et al. teach a method for detecting an isoprenylated protein (see col. 27, lines 14-15, "H-Ras farnesyl-group") in a cell (see col. 27, line 12, "oocytes") comprising the steps of: obtaining a synthetic isoprenyl (see col. 27, line 17, "farnesyl analogs") azide (see col. 6, line 52, "N<sub>3</sub>") substrate of a protein (see col. 26, line 3, "FTase"), contacting the cell under conditions wherein the cell takes up (see col. 27, line 18, "microinjection") and incorporates (see col. 27, lines 16-17, "enzymatic methods to attach"; col. 27, lines 29-30, "in vivo farnesylation of the injected H-Ras protein") into the protein (see col. 27, line 17, "H-Ras") a first azide (see col. 6, line 52, "N<sub>3</sub>") from the substrate (see col. 27, line 17, "farnesyl analogs"), and detecting (see col. 25, line 66, "Assay for Analog Transfer") said protein (see col. 26, line 3, "FTase").

Spielmann et al. do not teach the step of detecting said isoprenylated protein with "a phosphine capture reagent" or "the Staudinger reaction".

However, Saxon & Bertozzi teach the use of a phosphine capture reagent and the Staudinger reaction for detecting intracellular azido-target substrates (see col. 14, line 57, "detectable labels", line 55,

Art Unit: 1641

"intracellular", lines 52-53, "azido-target substrate"). Therefore, it would have been obvious for a person of ordinary skill in the art to perform the method for detecting an isoprenylated protein, as taught by Spielmann et al., with a phosphine capture reagent and the Staudinger reaction because Saxon & Bertozzi discovered that the Staudinger reaction is both selective and compatible with aqueous environments, which allows for *in vivo* applications (see Abstract).

With respect to claim 3, Spielmann et al. teach a method wherein the first protein is isolated (see col. 24, line 34, "farnesylated p<sup>21H-ras</sup> on SDS-polyacrylamide gel").

With respect to claims 4-6, Spielmann et al. teach a method wherein FPP is inhibited with lovastatin (see col. 27, line 49, "mevinolin").

With respect to claims 7 and 9, Spielmann et al. teach a method comprising an azido farnesyl diphosphate (see col. 27, line 35, "FPP analogues", col. 6, line 52, "N<sub>3</sub>").

With respect to claim 11, Spielmann et al. teach a method wherein the first protein is native to said cell (see col. 27, line 32, "FTase in oocytes").

With respect to claims 13 and 20, Saxon & Bertozzi teach a method wherein the phosphine is bound to a solid support comprising an inorganic bead (see col. 17, line 28).

With respect to claims 15-16, Saxon & Bertozzi teach a method wherein the phosphine comprises a fluorescent label (see col. 16, lines 55-67).

With respect to claims 17-19, Saxon & Bertozzi teach a method wherein the phosphine comprises biotin reaction with avidin (see col. 15, lines 8-9).

Art Unit: 1641

With respect to claims 21-22, Saxon & Bertozzi teach a method wherein a nucleophile is immobilized on a polysaccharide (see col. 13, lines 4-5).

With respect to claim 23, Spielmann et al. teach a method wherein the synthetic prenyl azide substrate is a substrate for a plurality of proteins (see col. 1, lines 59-67, "FTase", "CAAX GGTase", "Rab GGTase").

---

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Spielmann et al. (US 6,284,910) and Saxon & Bertozzi (US 6,570,040) as applied to claim 1, and further in view of Lodish et al., MOLECULAR CELL BIOLOGY, 4th ed., W.H. Freeman & Co. (1999).

Spielmann et al. and Saxon & Bertozzi teach a method for detecting an isoprenylated protein as substantially described supra. The aforementioned references do not teach Western blot detection.

However, Lodish et al. teach the use of Western blot detection for detecting a particular protein in a complex mixture (see Section 3.5). Therefore, it would have been obvious for a person of ordinary skill in the art to perform the method for detecting an isoprenylated protein, as taught by Spielmann et al. and Saxon & Bertozzi, with Western blot detection because Lodish et al. teach Western analysis is "one of the most powerful methods for detecting a particular protein" combining "superior resolving power of gel electrophoresis, the specificity of antibodies, and the sensitivity of enzyme assays."

---

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Spielmann et al. (US 6,284,910) and Saxon & Bertozzi (US 6,570,040) as applied to claims 1 and 13, and further in view of Holmes, 62 J. ORG. CHEM. 2370 (1997).

Art Unit: 1641

Spielmann et al. and Saxon & Bertozzi teach a method for detecting an isoprenylated protein as described supra. In addition, Saxon & Bertozzi teach the use of a cleavable linker (see Abstract). The aforementioned references do not teach the use of a photocleavable linker.

However, Holmes teaches the use of a photocleavable linker for anchoring biomolecules to solid supports (see Abstract). Therefore, it would have been obvious for a person of ordinary skill in the art to replace the cleavable linker of Saxon & Bertozzi with a photocleavable linker because Holmes states that photocleavable linkers are "particularly attractive in combinatorial library screening," as they result in biomolecules that are free of cleavage reagents (see p. 2370, col. 1, lines 11-18).

### ***Response to Arguments***

In prior Office Action, claim 1, step (a), was rejected under 35 U.S.C. 112, second paragraph, as being indefinite because it was not clear whether step (a) requires obtaining a first protein and/or a cell. In addition, the recitation of "a first protein" was considered indefinite because it was not clear whether "a first protein" corresponds to "a first isoprenylated protein" recited in the preamble. Applicants' amendment and argumentation are sufficient to overcome these rejections. Accordingly, these rejections are withdrawn.

In prior Office Action, claim 1, step (b), was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the recitation of "a first azide" because it was not clear whether "a first azide" corresponds to the "isoprenyl azide" of step (a), or whether "a first azide" describes a separate azide entity distinct from the "isoprenyl azide" of step (a). In addition, it was not clear whether "a first azide" and "substrate" are separate entities, or how "a first azide" and "substrate" become separate entities. In addition, the recitation of "contacting the cell" was considered indefinite because it was not clear what entity is



Art Unit: 1641

contacted with the cell. In addition, the recitation of "the protein" lacked antecedent basis and was considered indefinite because it was not clear whether "the protein" corresponds to "a first protein" recited in step (a) or "a first isoprenylated protein" recited in the preamble. In addition, the recitation of "the substrate" lacked antecedent basis and was considered indefinite because it was not clear whether "the substrate" corresponds to "a synthetic isoprenyl azide substrate" recited in step (a). Applicants' amendment and argumentation are sufficient to overcome these rejections. Accordingly, these rejections are withdrawn.

In prior Office Action, claim 1, step (c), was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the recitation of "said first protein" because it was not clear whether "said first protein" corresponds to "the protein" recited in step (b) or "a first isoprenylated protein" recited in the preamble. Applicants' amendment and argumentation are sufficient to overcome this rejection. Accordingly, this rejection is withdrawn.

In prior Office Action, claim 1 was rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps because the preamble of claim 1 did not appear to correspond to the method outcome. Applicants' amendment and argumentation are sufficient to overcome this rejection. Accordingly, this rejection is withdrawn.

In prior Office Action, claim 2 was rejected under 35 U.S.C. 112, second paragraph, for the recitation of "the protein is farnesylated" because it was not clear during which step(s) of claim 1 said protein is farnesylated. Claim 19 was rejected under 35 U.S.C. 112, second paragraph, because it was not clear how "affinity-purification" is incorporated into the method of claim 1. In claim 20, the recitation of "a bead" was considered indefinite because it was not clear whether a single bead is intended. In claim 21, it was not clear how "a nucleophile" is incorporated into the method of claim 1 or whether "a nucleophile" correlates to any entity recited in claim 1. In claim 24, the recitation of "the prenylated protein" lacked antecedent basis. In claims 25-26, the incorporation of "+" adjacent to the recited molecular formulas was

Art Unit: 1641

considered indefinite because it was not clear what chemical entity corresponds or correlates to "+". In claim 28, step (a) was considered grammatically awkward and indefinite because it was not clear whether "a synthetic substrate" comprises "a first azide", or whether "said protein" comprises "a first azide." Applicants' amendment and argumentation are sufficient to overcome these rejections. Accordingly, these rejections are withdrawn.

In prior Office Action, claims 4-6 were rejected under 35 U.S.C. 112, second paragraph, because the recitation of "FPP is inhibited" was considered indefinite. In response, Applicants argue that the term "inhibited" has well known meaning in the art. Applicants' amendment and argumentation are sufficient to overcome this rejection. Accordingly, this rejection is withdrawn.

In prior Office Action, claim 12 was rejected under 35 U.S.C. 112, second paragraph, because it was not clear how "Western blot analysis" is incorporated into the method of claim 1. Applicants' argumentation is sufficient to overcome this rejection. Accordingly, this rejection is withdrawn.

In prior Office Action, claim 29 was rejected under 35 U.S.C. 112, second paragraph, because the recitation of "synthetic" was considered indefinite. Applicants' amendment and argumentation are sufficient to overcome this rejection. Accordingly, this rejection is withdrawn.

---

In prior Office Action, claim 1, step (a), was rejected under 35 U.S.C. 112, second paragraph, because the recitation of "isoprenyl azide substrate of at least a first protein" was considered grammatically awkward and indefinite. In response, Applicants argue that it is clear from the language of the claim that "substrate" modifies protein and refers to a substrate of the protein (see Applicants' reply, p. 11, lines 11-12). Applicants' argument has been carefully considered but is not persuasive because it is not clear whether said "substrate" is a substrate for said "azide" entity. It is not clear whether/how said "substrate"

Art Unit: 1641

is simultaneously a substrate for both "azide" and "protein". It is not clear what protein(s) bind/catalyze "azide" substrate.

In prior Office Action, claim 1, step (b), was rejected under 35 U.S.C. 112, second paragraph, because the recitation of "incorporates into the protein at least a first azide" was considered indefinite. In response, Applicants have amended claim 1 to clarify that the first azide is incorporated into the protein. Applicants' amendment has been carefully considered but is not sufficient to overcome this rejection. It is not clear whether/how a protein "incorporates" an azide moiety. The synthetic mechanism or reaction conditions of incorporation are not clear. It is not clear whether an azide moiety is synthesized *de novo* intracellularly on "the first protein". It is not clear whether/what cells are capable of intracellular azidation.

In prior Office Action, claim 1, step (c), was rejected under 35 U.S.C. 112, second paragraph, because the recitation of "proteins produced by said cell with a phosphine capture reagent" was considered indefinite. In response, Applicants argue that the phrase "with a phosphine capture reagent" modifies "detecting" and not "produced by said cell" (see Applicants' reply, p. 13, lines 10-12). Applicants' argument has been carefully considered but is not persuasive because step (c) appears to recite four consecutive prepositional phrases (i.e. "from proteins produced", "by said cell", "with a phosphine capture reagent", "by the Staudinger reaction"). The scope of step c) is indefinite unless the adjective and/or adverbial capacity of each prepositional phrase is established and related to every noun and/or verb.

In prior Office Action, claims 4-6 were rejected under 35 U.S.C. 112, second paragraph, because the recitation of "FPP" lacked antecedent basis. In response, Applicants argue that FPP is naturally produced by cells, is inherently present in a cell, thus has antecedent basis in "cell". Applicants' argument has been carefully considered but is not persuasive. Examiner posits that the acronym "FPP" is not established in the art to an extent necessary for definite recognition as farnesyl pyrophosphate (FPP). The issue of whether cells have antecedent basis for claim language appearing on paper appears beyond the scope of this Examiner.

Art Unit: 1641

In prior Office Action, claims 5-6 were rejected under 35 U.S.C. 112, second paragraph, because it was not clear how "HMG Co-A reductase inhibitor" and "lovastatin" inhibit FPP. In response, Applicants argue that it is not necessary to recite the details of FPP inhibition by HMG Co-A reductase inhibitor and lovastatin because such details are known in the art and not required for the function and use of Applicants' claimed method. Applicants' arguments have been carefully considered but are not persuasive because, according to Applicants' reply, Lovastatin, a HMG CoA reductase inhibitor, blocks mevalonate synthesis, which leads to inhibition of FPP synthesis. Thus, it appears that claims 5-6, which merely recite "FPP is inhibited" appears mechanistically inaccurate/indefinite.

---

In prior Office Action, claims 1-7, 9 and 11-24 were rejected under 35 U.S.C. 103(a) in view of Spielmann et al. (US 6,284,910) and Saxon & Bertozzi (US 6,570,040). In response, Applicants argue that persons of ordinary skill would not have motivation to combine Spielmann et al. with Saxon & Bertozzi because the teachings of Spielmann et al. are directed to therapeutic applications, rather than the detection of isoprenylated protein in a cell (see Applicants' reply, p. 20, lines 5-6, "Spielmann concerns a specific FPP analog and therapeutic implications of this rather than detecting an isoprenylated protein in a cell as claimed"). Applicants' argument has been carefully considered but is not persuasive because the teachings of Spielmann et al. are not so limited to therapeutic applications. The teachings of Spielmann et al. also include a description of a synthetic scheme for making isoprenyl azide substrates (see e.g., col. 12, Scheme 1), as well as several methods for their direct detection (see col. 25, lines 18-19, "ethanol-HCl precipitation and scintillation counting"; col. 24, lines 32-34, "incorporated radioactivity... on SDS-polyacrylamide gels"; col. 24, lines 51-52, "reverse phase chromatography"; col. 25, line 66, "Continuous Fluorescence Assay"). Thus, it appears that the teachings of Spielmann et al. complement the teachings of Saxon & Bertozzi, who teach that azido-target substrates can be detected using phosphine capture reagents and the Staudinger reaction. Saxon & Bertozzi provide further motivation by describing the

Art Unit: 1641

discovery that the Staudinger reaction is both selective and compatible with aqueous environments, which allows for *in vivo* applications (see Abstract).

Examiner notes that col. 28-29 of Spielmann et al., referencing "continuous fluorescence assay for analog transfer", is no longer cited in *Claim Rejections - 35 USC § 103* in the instant Office Action. Its further discussion has been rendered moot.

Finally, Applicants claim that Spielmann et al. describe a microinjection technique that does not involve a substrate of H-Ras (see Applicants' reply, p. 21, lines 6-14). Nonetheless, Examiner observes that Spielmann et al. appear to describe a microinjection technique wherein injected H-Ras protein is farnesylated *in vivo* (see col. 27, lines 29-30, "in vivo farnesylation of the injected H-Ras protein"). Thus, it appears that Spielmann et al. continue to describe step b) of Applicants' claimed invention.

Art Unit: 1641

**Conclusion**

Claims 25-29 appear free of the cited prior art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Venci whose telephone number is 571-272-2879. The examiner can normally be reached on 08:00 - 16:30 (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

David J Venci  
Examiner  
Art Unit 1641

djv



LONG V. LE  
SUPERVISORY PATENT EXAMINER  
TECHNOLOGY CENTER 1600

09/06/07